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### CONDITIONAL PETITION FOR EXTENSION OF TIME

If any extension of time for this response is required, Applicants request that this be considered a petition therefore. Please charge the required fee to Deposit Account No. 14-1263.

### ADDITIONAL FEES

Please charge any further insufficiency of fees, or credit any excess to Deposit Account No. 14-1263.

### REMARKS

Entry of the amendment and consideration of the remarks are respectfully requested.

The amendment of claim 32 overcomes the anticipation by Suzuki. The amendment, does not raise new issues or add new matter.

New claim 34 is the same as claim 32, wherein the additional components are required, not optional. New claim 34 also includes a functional limitation directed toward the specific cellular effects of the active agents. Claim 34 is not anticipated by Suzuki or by Raff.

New claims 35-36 add similar limitations reciting the cellular effects of the composition.

Claims 32-33 are rejected as allegedly being anticipated by US '781 to Suzuki.

Claims 25-31 are rejected as allegedly being anticipated by US '912 to N'Guyen.

Claims 19-29 are rejected as allegedly being obvious over US '171 to N'Guyen in view of Middleton and Harrison.

Claims 19-33 are rejected as Examiner believes the claims unpatentable for obviousness-type double patenting over claims 1 and 4 of US '373 and claims 1-5 of US '243. Claims 19-33 are provisionally rejected on the same basis in view of Applications 09/656598 and 09/540007.

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Claims 32-33 are reject d as allegedly being anticipated by US '343 to Raff.

Preliminary Remarks in Response to Examiner's Comments

Harrison in Combination with N'Guyen and/or Suzuki

In the Advisory Action of 7 October 2003, Examiner states that Applicants' argument in support of the claims' allowability "does not give any weight to the teachings of Harrison." Examiner also responds to the argument based on the contrary teachings of Middleton and N'Guyen that Applicants are arguing against the references individually rather than their combination.

Harrison discloses that UV irradiation is a cause of immunosuppression. Harrison further discloses that this immunosuppression is likely to result from the deleterious effects of UV on antigen presentation. Applicants acknowledge that Harrison may be useful for broadly teaching that UV irradiation may cause immunosuppression.

However, Harrison does not teach or suggest that any flavonoids, let alone those specifically claimed will protect against UV-induced immunosuppression. Examiner has apparently concluded from Harrison that any sunscreen formulation will possess this property. In response, it is pointed out that Harrison's teachings, taken individually or in combination with the other references, reach no more than an obvious to try standard, which is below the threshold necessary to maintain an obviousness rejection.

This is because none of the applied references teach or suggest that the claimed compositions can be used in a method to prevent UV-induced immunosuppression. It is not even remotely sufficient that N'Guyen and Suzuki disclose that some flavonoids may have anti-oxidant properties, as the claims are far more focused on immunosuppression, not anti-oxidant properties.

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Middleton in Combination With the Applied References

In the final action, as well as in the office action of May 22, 2002, Examiner applied the article of Middleton for demonstrating the state of the art. However, Examiner has inaccurately not properly interpreted Middleton's disclosure, and a result, cannot have conceptually combined its teachings with those of N'Guyen, Suzuki and Harrison.

Examiner's belief that the Applicants' analysis of Middleton is deficient because it the rejection is based on the combination of references does not take into consideration [a] Examiner's own reason for asserting Middleton, and [b] the substantially mischaracterized interpretation of its teachings.

Examiner acknowledged Middleton's "*plethora of information about the effects of flavonoids on the immune system.*" Office action 5/222002, page 8.

If nothing else, Middleton is the only reference of record that deals with immunity and flavonoids. Thus, Middleton, *even by itself*, represents the pivotal link between flavonoids and Harrison's overbroad and nonenabling discussion of UV and immunosuppression.

It is indisputable that the sum total of Middleton's discussion of the effects of flavonoids on T-cell activity predicts that flavonoids would suppress T-cell function, and therefore enhance immunosuppression. As such, Middleton's disclosure (pp. 625-628) teaches away from (1) the claimed method, and (2) Examiner's interpretation of the combined teachings of N'Guyen, Harrison and Middleton.

In the office action of May 22, 2002, Examiner correctly, albeit selectively, refers to Middleton's teaching that genistein inhibits T-lymphocyte protein tyrosine kinase activity. See office action, page 8. However, Examiner then incorrectly concludes that such stimulation leads to immunosuppression, while Middleton concludes the opposite.

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In fact, reviewing Middleton's relevant disclosure as a whole, it is clear that the overwhelming portion of the data presented indicates that flavonoids actually augment immunosuppression. Thus, based on Middleton's teachings, alone or in combination, the obviousness rejection should be withdrawn. MPEP § 2144.02 (A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention; citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1983).

The Fed Circuit has even more emphatically stated that "references cannot be combined where reference teaches away from their combination." MPEP § 2145. It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 218 USPQ 769, 779 (Fed. Cir. 1983).

A portion of Middleton's disclosure is presented below.

- § Genistein inhibits the protein kinase, p56<sup>lck</sup>, thus inhibiting T-cell stimulation as evidenced by reduced interleukin production. Reducing cytokine production is known to diminish the immune response and, therefore, enhances immunosuppression. Page 625, col. 2, 1st paragraph.
- § Genistein was explicitly disclosed as having immunosuppressive properties in experiments relating to graft rejection reactions. Page 625, col. 2, 2nd paragraph. Middleton concludes "[t]he potential use of genistein as an immunosuppressive agent together with cyclosporine in allograft rejection was suggested."
- § Quercetin inhibits another protein tyrosine kinase found in human plasma. Page 625, col. 2, 3rd paragraph
- § PI kinase, an enzyme that generates phosphatidyl inositolphosphates as second messengers involved in T-cell activation, can be inhibited by various flavonoids.

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See Page 626, col. 1, 1st paragraph. Inhibiting T-cell activation is very likely to lead to immunosuppression.

- ξ Protein kinase C, known to be involved in T-cell activation is inhibited by flavonoids. Page 626, col. 1, 2nd paragraph. Inhibiting T-cell activation is very likely to lead to immunosuppression.
- ξ Middleton discloses that several downstream effectors in T-cells may be inhibited by flavonoids. Page 626, col. 1, 3rd paragraph. Thus, inhibiting T-cell function enhances immunosuppression.
- ξ Flavonoids blocked activation of T-cells via the CD3 T-cell Receptor. Page 626, col. 2, 2nd paragraph. One in the art would understand that inhibition of T-cell activation may lead to immunosuppression.
- ξ Flavonoids depressed the expression of class II histocompatibility antigens. Page 627, col. 1, 1st paragraph. This clearly enhances immunosuppression by inhibiting antigen presentation to T-cells, and thus, block T-cell activation.
- ξ Flavonoids inhibit lymphocyte proliferation in response to mitogens. Inhibiting lymphocyte proliferation clearly promotes immunosuppressive effects. Page 627, col. 1, 1st paragraph.
- ξ Various flavonoids have been shown to inhibit the development of cytotoxic lymphocytes as well as their specific functions. Page 627, col. 2, 2nd paragraph.
- ξ Flavonoids inhibited the immune response to sheep erythrocytes *in vitro*. Page 627, col. 1, 3rd paragraph.
- ξ Various flavonoids inhibit spleen cell proliferation in response to T-cell presentation of a mitogen. Page 627, col. 1, 3rd paragraph.

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- § A unique flavonoid inhibited various mitogen-induced effects on various cells of the immune system. Page 627, col. 1,3rd paragraph.

Respectfully, in view of this disclosure, persons of ordinary skill in the art could not reasonably be expected to view flavonoids as preventing immunosuppression. Thus, there is no suggestion to combine Middleton with Harrison and N'Guyen to support a rejection under § 103.

Examiner's Specific Reliance on the Scientific Evidence

The following specific examples are provided to illustrate how the Middleton reference has been improperly applied in maintaining the rejections.

Examiner attempts to support his position by citing Okada et al., in Middleton, page 627, 2nd col.[sic] (should be first column) that shows "quercitin has been effective in regressing the spread of fibrosacroma." Office action, 5/22/2003, page 8. However, if the relevant text is read in its entirety, it clearly states that it was only the fibrosarcoma cells that were treated with quercitin, not the T-lymphocytes or the whole mice. Consistent with this is Okada's disclosure that the flavonoid-treated fibrosarcoma cells were cloned out to allow selection of new colonies that were no longer inherently immunogenic. Thus, flavonoids induced fibrosarcoma clones that lacked the antigen. Page 627, col. 1, 2nd ¶].

Further, these experiments indicate that Okada shows that quericitin results in a greatly diminished immune response – the opposite of what is claimed. Thus, Okada directly contradicts Examiner's rationale for combining N'Guyen and Harrison (discussed below).

In the same office action, Examiner asserts that "*topical quercitin has been effective in preventing and improving various immunosuppressive conditions associated with skin cancer (see pp 642, 3rd-8th).*" This statement is not explicitly or impliedly supported by the facts in the cited text.

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ξ The cited text does not even discuss immune responses at all. Examiner's belief that all tumors grow due to immunodeficiency is not accepted in the art, and is not disclosed here.

ξ A cursory reading would have indicated that the proposed mechanisms for these effects did not relate to immunology at all. The proposed explanations ranged from not knowing, to effects on enzyme systems that are known to activate chemical carcinogens; most notably the P-450 family.

The misinterpretation of the art has been key in maintaining the rejections, and therefore, it is also critical in arguing for their withdrawal.

It is respectfully requested that Examiner consider the foregoing remarks when evaluating the comments in support of withdrawing the rejections.

Anticipation by '781 to Suzuki

In the final action, Examiner correctly states that claims 32-33 encompass a cosmetic or dermatologic composition comprising glucosylrutin. Final action, section 3.

In response, Applicants have amended claim 31, by deleting *glucosylrutin*. Accordingly, Suzuki does not anticipate claims 31 and dependent claim 32.

Anticipation by '912 to N'Guyen

Examiner Asserts an Undisclosed and Unsupported Scientific Theory  
to Maintain the Rejection

The Examiner indicates that the '912 explicitly discloses topical application of N'Guyen's compositions to protect the skin from oxidation, and therefore anticipates the claims. See final action, section 7. Respectfully, this argument is not logical or technically sound, and therefore, is not legally sufficient to maintain the rejection. MPEP § 2144.02.

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The cited text (col. 5, lines 59-61) expressly states that topical applications of N'Guyen's compositions, in particular in cream form, are "intended to protect the lipids of the skin from oxidation." In no way can this intended effect conceptually or medically linked to the claimed method of preventing immunosuppression.

Examiner apparently assumes without evidence or sound technical reasoning, that oxidation of lipids in the skin results in immunosuppression. N'Guyen does not disclose this. Further, neither Harrison nor Middleton fill this gap.

N'Guyen does not use the term "immunosuppression" or immuno-anything. Thus, it is not proper to assert N'Guyen's composition as anticipating method claims for treating immunosuppression.

Examiner seems to assert his own theory that immunosuppression results from lipid oxidation. The MPEP explicitly requires that "evidentiary support for the existence and meaning of that theory must be provided." *In re Grose*, 201 USPQ 57 (CCPA 1979). Without such evidence, the basis for rejecting the claims is not supported. MPEP § 2144.02.

In view of the complete omission of the subject of immunosuppression by N'Guyen, it is not plausible that any aspect of his disclosure anticipates claims for the treatment of immunosuppression.

Withdrawal of the rejections under § 102 are respectfully requested.

Examiner Apparently Relies on an Inherency Theory

In view of the lack of support for the existence of a connection between lipid oxidation in the skin and immunosuppression, Examiner may believe that topical application of N'Guyen's cream will inherently prevent immunosuppression. If so, it is respectfully pointed out that the legal standard for rejecting claims on an inherency theory is quite clear.



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"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (Emphasis added). MPEP § 2112.

"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). MPEP § 2112. (Emphasis added).

It is clear that in order for N'Guyen to anticipate the claims, Examiner must supply evidence demonstrating that his proposed treatment with N'Guyen's cream would necessarily have produced an anti-immunosuppression effect. It is suggested that no such evidence was presented. Further, as discussed below, no such evidence was available at the time of Applicants' filing date.

Applicants respectfully point out the foregoing discussion of Middleton's article, to indicate that any notion that flavonoids necessarily result in immunosuppression cannot be correct.

In accordance with the foregoing remarks, Applicants respectfully request withdrawal of all anticipation rejection over the '912 patent to N'Guyen.

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Obviousness Over '171 to N'Guyen in View of the Articles by Middleton and Harrison

N'Guyen's disclosure is directed to finding alternatives to ascorbate as an antioxidant to prevent oxidation of lipid-containing cosmetic and dermatological formulations. In other words, he is primarily concerned with preserving the product's properties during storage; i.e., to increase its shelf-life. See N'Guyen '171, col. 1 lines 12-53. Among the problems disclosed are oxidation associated changes in the aromatic/olfactory properties (line 17) and, general preservation during storage (lines 42-45). N'Guyen then also discusses the potential benefits to prevent oxidation of skin lipids. Col. 1 lines 54-58.

Although N'Guyen discloses a potential benefit to the skin by preventing lipid oxidation, it is a grossly unjust reading of this reference and unsupported leap of logic for Examiner to suggest that N'Guyen '171 even remotely or impliedly discloses any benefits to the immune system. Final action, page 5-6.

Further, as discussed at length with respect to Middleton's disclosure of the art, persons of ordinary skill could not read the combined references and extract the conclusion that N'Guyen's compositions could attenuate immunosuppression, with a reasonable expectation of success.

After a brief discussion of N'Guyen's disclosure, Examiner asserts that "one of ordinary skill in the art would deduce that topical or cosmetic application of N'Guyen's compositions would provide antioxidizing effects including protecting the lipids of the skin. Thus, protecting lipid of the skin from oxidation and subsequent damage would attenuate immunosuppression to the extent that it falls within the scope of the instant pending claims." Final action, page 5. Examiner's rationale seems based more on his own theory of immune suppression than what is disclosed in the references.

Middleton clearly indicates that extrapolating from N'Guyen's disclosure that flavonoids may inhibit the oxidation of skin lipids, to result in the attenuating of

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immunosuppressive conditions, is to ignore the bulk of evidence to the contrary. Such a connection cannot be found in any of the references including N'Guyen, Middleton and/or Harrison, and therefore is not a theory known in the art.

Examiner also asserts that the only teachings lacking by N'Guyen is "an explicit statement about beneficial effects of flavonoids on the immune system." Final action, top page 6. This is not correct and further mischaracterizes N'Guyen's disclosure. There is not even an implicit statement about the effects of topically applied flavonoids on the immune system. Examiner's mere belief that lipid oxidation *necessarily* effects the immune system is unsupported speculation that is not within the prior art and cannot be a basis to maintain a rejection.

Just as important, the teachings of Middleton and Harrison cannot fill the missing gaps.

~~N'Guyen in View of Middleton/Harrison Enable the Claimed Method and Do  
Not Render the Claims Obvious~~

The claimed subject matter, including that newly added and amended herein, are supported by experimental evidence showing the specific nature of the activity of the composition's key ingredients.

It is well established that a proper reference under 35 USC§§102 or 103 must be enabling in the sense of 35 USC § 112, paragraph 1. It is suggested that the cited references are not enabling to that extent. Pertinent is the following quote from *In re Le Grice*, 133 USPQ 365, 374 (CCPA 1962):

The proper test of a description in a publication as a bar to a patent as the clause is used in section 102(b) requires a determination of whether one skilled in the art to which the invention pertains *could take the description of the invention in the printed publication and combine it with his own knowledge of the particular art and from this combination be put*

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*in possession of the invention* on which a patent is sought." [Emphasis added]

The references do not reach this level of enablement. The references do not disclose, or even support a conclusion that flavonoids may counter immunosuppression.

The references are completely devoid of any guidance showing that flavonoids may have effects directly on antigen presenting cells and/or lymphocytes. Thus, the newly amended and added claims cannot reasonably be considered obvious in view of the references.

New Ground for Rejection - Anticipation Over Raaf

This rejection has been overcome by the foregoing amendment.

Claim 32 no longer recites hesperidin.

New claim 34 requires at least one cinnamic acid derivative and at least one non-flavonoid anti-oxidant.

CONCLUSIONS

Allowance of the claims is respectfully requested.

The references do not, individually or in combination, teach or suggest all of the claim limitations. In fact they do not provide for the core of the claimed subject matter.


The Middleton reference clearly indicates that the role of flavonoids in immunosuppression as applied by the Examiner is inaccurate. The overwhelming majority of disclosed results indicates that flavonoids are likely to act by enhancing immunosuppression. Thus, the combination of N'Guyen in view of Harrison and Middleton do not support the instant rejection.

Allowance of the claims is requested.

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